Science 24 March 2006:
Vol. 311. no. 5768, pp. 1688 - 1689
DOI: 10.1126/science.311.5768.1688

NEWS OF THE WEEK

DRUG TRIALS:
Violent Reaction to Monoclonal Antibody Therapy Remains a Mystery

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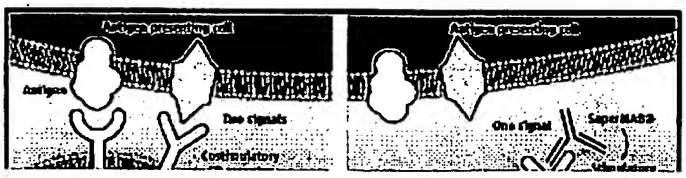
CAMBRIDGE, U.K.—It took only minutes to realize that something had gone seriously wrong. On 13 March, six healthy volunteers in a clinical trial were injected with a "superagonist," a drug meant to boost a type of T cell in the immune system, and soon all of them became violently ill. According to relatives and friends last week, the six vomited, collapsed, and passed out; one became bloated "like the Elephant Man," his girlfriend told the press. Two additional participants who had received a placebo showed no ill effects.

The volunteers were paid to participate in the trial (according to one, about $3460), the first human tests of a drug aimed at treating leukemia and autoimmune diseases such as multiple sclerosis and rheumatoid arthritis. They were given a synthetic (monoclonal) antibody called TGN1412, designed by TeGenero in Würzburg, Germany, and manufactured by Boehringer Ingelheim. In animal tests, the molecule triggered the production of so-called regulatory T cells, which keep the immune system in check. But something went amiss. The worst-affected volunteers were kept alive with mechanical life support and large doses of steroids to reduce inflammation. After 5 days, a doctor at Northwick Park Hospital near London said four were improving and three had been removed from machines. But the two worst affected remained in critical condition early this week.

Exactly what triggered the reaction is not known. It seemed at first that an error in drug dosing or manufacture may have been to blame, says Simon Gregor, spokesperson for the U.K. Medicines and Healthcare Regulatory Authority (MHRA), which approved the trial. Managers at Northwick Park were so surprised that they even called in the police to check for evidence of a crime. But as MHRA and other investigators analyze materials and swarm over the private, 36-bed ward where the test took place, no crime or technical error has come to light. Suspicion is focusing instead on TGN1412 itself.



Strong medicine. The human T cell, a multitasking agent in the

immune system, is normally activated only when two receptors are stimulated (*left*). But the "superagonist" used in a London clinical trial can activate T cells by stimulating a single receptor (*right*).

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Roulette. Six healthy volunteers injected with a test drug had to be rushed into critical care at Northwick Park Hospital; two others injected with a placebo weren't affected.

CREDIT: KIRSTY WIGGLESWORTH/AP PHOTO

MHRA, TeGenero, and the company that managed the trial, Parexel in Boston, Massachusetts, say that their procedures still look watertight. The volunteers' reactions were unforeseeable, they maintain. TeGenero's chief scientific off icer Thomas Hanke expressed "shock" in a statement on 17 March: "Extensive preclinical tests showed no sign of any risk."

Hanke told *Science* that a rodent version of the molecule was tested extensively at high doses in rats and mice, with no ill effects; TGN1412 itself was given to 20 cynomolgus monkeys in an unpublished study--after it was shown that their T cells were activated in the same way as human cells--with no significant adverse effects other than a short-lived increase in lymph node size. MHRA's Gregor says, "We have gone back [to the files] this week, and there is nothing in the documentation that would cause us to think there is a concern here."

But some independent observers have suggested that the trial was moving too aggressively. It was "a mad concept" to give a potent drug never tested in humans to six people at once, says medicines policy expert Joe Collier of St. George's Hospital Medical School in London. It would have been better to do one test and pause, he says. Monoclonal cancer vaccine researcher Angus Dalgleish of St. George's agrees that the procedure looks "bizarre," because the results of T cell activation are notoriously hard to predict.

Hanke responds that the trial's approach was "fairly common," reflecting "current practice in biopharmaceutical development." He adds: "We did not have any evidence to suspect that this drug would be unsafe at the dosage we applied," which was, at 0.1 milligram per kilogram of weight, one-500th that given as a safe dose in animals.

Some also question TeGenero's decision to move into human testing without a better developed--or at least a more publicly documented--rationale for how TGN1412 could up the count of regulatory T cells without turning on other, destructive responses. TeGenero's co-founder and scientific adviser Thomas Hünig of Würzburg University says that research since 1997 has shown that TGN1412 and analogous antibodies bind to the CD28 receptor on T cells, triggering a powerful expansion of cells dominated by regulatory T cells. Even at "horrific" doses in rats and mice, he says, regulatory cells dominated, giving credence to the view that these cells' damping effect would swamp out the more harmful effects of conventional T cells, also activated by TGN1412. The monkey study supported this confidence, says Hanker: "We saw no drug-related adverse events."

Some experts in monoclonal antibodies–including Dalgleish and Arlene Sharpe and David Hafler of Harvard Medical School in Boston, as well as John Isaacs of the University of Newcastle, U.K.–say that without having seen the relevant monkey data or results from tests with human cells in vitro, it's difficult to evaluate the argument that TGN1412 would likely have the same selective, benign effect in humans as in test animals. But they say they would not be surprised to find that TGN1412 stimulates harmful as well as beneficial effects. "A lot of cells" carry the CD28 receptor and might be activated, Hafler notes, adding, however, that "I wouldn't have thought [an accident like this] could happen."

Johannes Löwer, president of the Paul Ehrlich Institute in Langen, Germany, says his center was also approached by TeGenero to assess the TGN1412 trial. "We reviewed it very carefully" and reached the same conclusion as the U.K. group: The trial was safe and should proceed. Löwer offers two lessons for the future. Research is needed to define better animal models of the human response to CD28 agonists, he says. And he recommends that extra precaution be taken when antibodies are used to stimulate rather than neutralize components of the immune system.

With reporting by Gretchen Vogel in Berlin.